REMARKS

Telephone Interview

Applicants' representative contacted Examiner Kim to discuss the Advisory Action, dated July 20, 2006, since it was not clear whether the response, dated June 19, 2006, was entered and whether the Information Disclosure Statement (IDS) submitted with the response was considered by the Examiner. The Examiner informed Applicants' representative that the response was not entered and the IDS was not considered and that the Examiner will consider the IDS if another response were filed. The rejections under 35 U.S.C. §§ 102(b) and 103(a) were also discussed, but an agreement was not reached.

Interview

Applicants would like to thank Examiner Kim and Supervisory Examiner Chan for their time spent in discussing this application. During the interview, Examiner Chan suggested amending the claims to distinguish the claimed invention over the cited references. Also, Applicants explained the results of Table 13 in the specification to overcome the enablement rejection. The Examiners agreed to consider the explanation when submitted in writing in response to the Office Action. This response incorporates the suggestion for amending the claims and the explanation of the results of Table 13 discussed during the interview

Information Disclosure Statement

Applicants respectfully request that the Examiner consider the Information Disclosure Statement (under 37 CFR 1.97(c)(1)) submitted on June 19, 2006.

Amendments to the Specification

The specification has been amended to update the status of the related applications and to correct inadvertent typographical errors. The amendment to the specification does not introduce prohibited new matter.

Status of the Claims

Claims 162-256 are currently pending in the present application. Claims 1-161 have been

canceled without prejudice or disclaimer of the subject matter claimed therein. New claims 162-256 have been added. Representative support for new claims 162-256 can be found in the table below. The new claims do not introduce prohibited new matter.

Claim(s)	Representative Support
162	Claim 106; Page 3, lines 29-31
163, 195	Claim 107
164, 196	Claim 109
165, 197	Claim 110
166, 198	Claim 111
167, 199	Claim 112
168, 200	Claim 113
169, 201, 233	Page 8, lines 29-31; Page 7, lines 7-10
170, 202, 234	Claim 114
171, 203, 235	Pages 24-26
172, 204, 236	Claim 115; Page 24, line 26
173, 205, 237	Claim 116
174, 206, 238	Claim 117; Page 25, line 22
175, 207, 239	Claim 118
176, 208, 240	Claim 118; Page 7, lines 7-10
177, 209, 241	Page 9, line 26 and pages 24-26
178, 210, 242	Claim 115; Page 24, line 26
179, 211, 243	Page 9, lines 8-10
180, 212, 244	Claim 115; Page 24, line 26
181, 213, 245	Claim 116
182, 214, 246	Claim 117; Page 25, line 22
183, 215, 247	Claim 118
184, 216, 248	Page 23, line 16
185, 217, 249	Claim 119

186, 218, 250	Page 9, lines 15-18
187, 219	Claim 120
188, 220	Claim 121
189, 221	Claim 123
190, 222, 251	Page 9, lines 15-18; Page 26, line 23 to Page 27, line 32
191, 223, 252	Page 32, line 13
192, 224, 253	Page 5, line 1
193, 225, 254	Page 6, lines 1-5
194	Claim 124
226	Claim 142
227	Claim 143
228	Claim 145
229	Claim 146
230	Claim 147
231	Claim 148
232	Claim 149
255	Claim 161
256	Claim 159

Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph

Claims 142-159 and 161 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Claims 142-159 and 161 have been canceled and replaced with new claims 226-256. New claim 226 is directed to a method of inducing an antigen-specific immune response. New claims 227-256 are dependent upon claim 226 and therefore include all the limitations of claim 226.

The Office Action, dated April 24, 2006, alleges that the specification does not enable a method of inducing an immune response comprising applying a formulation to more than one application area including any area of the skin comprising a first parenteral administration followed by a transcutaneous application and cites the factors of *In re Wands* in support of its

position.

As discussed in the response submitted March 24, 2006, the specification describes in detail multiple applications of formulations comprising antigen and/or adjuvant to an area of skin (pages 8, lines 6-19; page 31, lines 12-15; and Examples 12, 13, 18, and 20). Specifically, the specification discloses parenteral delivery of a formulation followed by transcutaneous immunization to boost or prime an immune response induced by parenteral delivery (page 8, lines 11-15 and page 31, lines 12-15). As an example, Example 12 teaches intramuscular injection of DT to the hind thigh of mice followed by transcutaneous immunization of DT toxoid and CT, as the adjuvant, to the back of mice. Table 12 summarizes the results of Example 12 and shows that transcutaneous immunization is useful in boosting or priming an immune response induced by other routes of delivery. Specifically, Table 12 shows that mice (#8568 to #8572) who received intramuscular injection of the antigen followed by transcutaneous immunization of the antigen and adjuvant induced an immune response that is 60 times higher than that of mice (#8563 to #8567) who received only an intramuscular injection of the antigen. Also, mice (#8568 to #8572) induced an immune response that is about 1.8 times higher than that of mice (#8558 to #8562) who received three intramuscular injections of antigen.

The Advisory Action, dated July 20, 2006, alleges that multiple applications of different areas would not result in the same draining lymph nodes and points out that Example 12 discloses intramuscular injection in the thigh and transcutaneous immunization at the back of mice. Applicants respectfully submit that although Example 12 confirms that the parenteral injection and the transcutaneous immunization need not be at the same site to induce an immune response, the claims as they stand are directed to administering the separate formulations to the same area of the skin.

Moreover, Example 13 discloses multiple applications of formulations at different sites and at the same site of an animal to induce an antigen-specific immune response. Specifically, in Example 13, mice were transcutaneously immunized at the right ear and the left ear or only at the left ear. As shown in Table 13 (page 64), Group A mice transcutaneously immunized with antigen (BSA) at one ear and adjuvant (CT) at the other ear developed an immune response to the antigen that is 30 times higher than Group G mice immunized with antigen only in the left ear. Likewise, Group C mice transcutaneously immunized with antigen and adjuvant in the left

ear developed an immune response to the antigen that is 400 times higher than Group G mice. Although the immune response of Group A mice is lower than that of Group C mice, the immune response of Group A is significant. Moreover, the claims only require that there be an antigen-specific immune response. In summary, the results of Example 13 show that transcutaneous immunization of antigen and adjuvant at different sites and at the same site of an animal induces an antigen-specific immune response.

The Office Action, dated April 24, 2006, alleges that Example 13 does not teach parenteral delivery. However, Example 12 (page 60) describes parenteral delivery of a first formulation followed by transcutaneous immunization of a second formulation at a different site, as discussed above and in the response submitted on March 24, 2006.

Additionally, as discussed in the previous response dated March 24, 2006, Frech *et al.* confirm that an adjuvant, such as LT, administered as an immunostimulant patch on the skin subsequent to an influenza vaccination, improved influenza immune responses in the elderly (see Frech *et al.* Vaccine 23 (2005) 946-950). Frech *et al.* report that elderly adults who received intramuscular injection of an influenza vaccine containing HA followed by an LT patch placed 5 cm distal to the vaccine injection site showed enhanced immune response as compared to those elderly who only received vaccine injection alone (see Frech *et al.*: abstract, page 947, left column (last paragraph), Table 2). The report of Frech *et al.* supports the claimed invention of parenteral delivery of an antigen followed by application of a formulation comprising at least one adjuvant to the skin to enhance the immune response induced by the antigen.

With respect to the Wands factors cited in the Office Action, Applicants respectfully assert that given the teachings and data disclosed in the specification, the claimed invention is not unpredictable. A person of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation by following the teachings of the specification. The experimentation necessary to practice the claimed invention is only routine. Therefore, the specification provides sufficient guidance in the description of the invention and disclosed examples to enable a person of ordinary skill in the art to make and use the claimed method for inducing an antigen-specific immune response, in the absence of evidence to the contrary.

As pointed out in the previous response, the initial burden is on the Patent Office to provide a reasonable explanation as to why the scope of protection provided by the claims is not

adequately enabled by the disclosure. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Moreover, the court in *In re Marzocchi* stated that it is incumbent upon the Patent Office to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up its assertions with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Office Action has not provided a reasonable explanation as to why the claims are not enabled by the specification.

Rejection of the Claims Under 35 U.S.C. § 102(b)

Claims 106, 107, 109, 110, 114-121, 124, 125, 127, 128, and 132-129 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 95/17211 ('211), as evidenced by the Skills Checklist for immunization.

Claims 106, 107, 109, 110, 114-121, 124, 125, 127, 128, and 132-129 have been canceled and replaced with new claims 162-225. Claims 162 and 194 are directed to a method of inducing an antigen-specific immune response comprising pretreating or treating concurrently an area of the skin of a subject and applying a formulation transcutaneously to the treated area of the skin of a subject. Claims 163-193 and 195-226 are dependent upon claims 162 and 194, respectively.

The deficiencies of WO 95/17211 are discussed in the previous response dated March 24, 2006. In summary, the cited reference does not teach a method of inducing an antigen-specific immune response by applying a formulation transcutaneously to an area of the skin of a subject. The cited reference only teaches applying a formulation to mucosal surfaces of an organism, for example, oral or intranasal delivery of formulations comprising antigen and adjuvant, as discussed on page 1 lines 29-31 of the cited reference. In contrast, the presently claimed method involves transcutaneous immunization which comprises delivery of antigens and adjuvants into the outer layers of the skin and induction of an immune response. Moreover, delivery of antigens and adjuvants through the skin is different from delivery through mucosal surfaces because mucosal surfaces and the skin are structurally and functionally distinct tissues. Further, the cited reference requires the use of non-toxic mucosal adjuvants with the antigen for delivery to the mucosal surface. In contrast, a toxic adjuvant, such as CT, that cannot be used for mucosal delivery can be applied to the skin for transcutaneous immunization, the method of the present

invention.

The Office Action (dated April 24, 2006) and the Advisory Action (dated July 20, 2006) alleges that page 12, lines 12 and 13 of the cited reference teach applying the immunogenic composition transdermally. A review of '211 indicates that page 12, lines 8 and 16 describes that immunogenic compositions are conventionally administered parenterally and that "additional formulations" that are suitable for other modes of administration "include oral and pulmonary formulations, suppositories, and transdermal applications." As stated on page 12, lines 8-10, immunogenic compositions, at the time the published '211 application was filed, were administered parenterally. The published '211 application does not disclose administering immunogenic compositions transcutaneously. The statements in '211 that the Office Action referred to do not teach that immunogenic compositions can be administered transcutaneously.

The present invention is directed to transcutaneous immunization. As described in the specification, transcutaneous immunization requires both passage of antigen through the outer barrier (stratum corneum), which was thought to be impervious to such passage, and into the skin, and the induction of an immune response using the skin immune system (page 3, lines 29-31). In other words, transcutaneous immunization involve delivery of an antigen through the stratum corneum to antigen presenting cells, such as an epidermal Langerhans cells found in the skin, thus requiring the antigen to be delivered into the skin (page 16, lines 13-20). In contrast, transdermal delivery of immunogenic compositions as referred to in '211 requires delivery of the antigen through the skin and into the blood stream.

Moreover, Applicants respectfully submit that antigens in immunogenic compositions are macromolecules that could not be administered by applying to the skin of subject at the time '211 was filed. The background section of attached U.S. Patent 5,980,898 (priority filing date is November 14, 1996) describes the state of the prior art at the time '211 was filed. As discussed in U.S. Patent 5,980,898, in 1995, Paul *et al.* reported that the skin is an effective protective barrier that is impenetrable to molecules of greater than 750 DA, thus precluding non-invasive immunization with large immunogen through intact skin. Moreover, in 1995, Paul and Cevc stated, "Large molecules normally do not get across the intact mammalian skin. It is thus impossible to immunize epicutaneously with simple peptide or protein solutions." Accordingly, at the time '211 was filed, it was generally thought that large molecules such as CT or LT, which

are about 85,000 DA, can only be administered parenterally. Thus, '211 neither teaches nor enables applying transcutaneously an antigenic composition to the treated skin of a subject to induce an antigen-specific immune response as required by the claims of the present application.

Further, the court has held that for a reference to anticipate, the reference must enable the claimed invention. In *Minnesota Manufacturing and Mining v. Chemque, Inc.,* the Federal Circuit held that to anticipate a claim, a reference must also enable one of skill in the art to make and use the claimed invention. See *Minnesota Manufacturing and Mining v. Chemque, Inc.*, 303 F.3d 1294 (Fed. Cir. 2002). In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.,* the Federal Circuit stated that a claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). As discussed above, the cited reference only teaches mucosal delivery of antigens and adjuvants. The cited reference, '211, only generally states that additional formulations suitable for delivery by other modes of administration include transdermal applications. The cited reference does not describe in detail to enable applying transcutaneously an antigenic composition to the skin of a subject to induce an antigen-specific immune response.

The Office Action relies on the Skills Checklist for disclosing pretreatment of the skin by chemical means or by hydration means. The Advisory Action alleges that the Skills Checklist was supplied to show that pretreating the skin prior to immunization procedure is well known in the art. However, the claimed invention is directed to a method of inducing an antigen-specific immune response comprising applying an antigenic composition transcutaneously to the treated skin of a subject to induce the immune response. Neither '211 nor the Skills Checklist teaches applying transcutaneously an antigenic composition to the skin of a subject to induce an antigen-specific immune response.

In summary, the cited reference does not disclose the limitations required in the claims. The cited reference neither teaches delivery of an antigen by transcutaneous application to the skin of a subject nor discloses treating the skin prior to or at the same time as applying transcutaneously the antigen to induce an antigen-specific immune response.

Rejection of the Claims Under 35 U.S.C. § 103

A. Claims 106-108, 113, 122-126, 131, 140 and 141 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 95/17211 ('211) as evidenced by Skill Checklist for immunization in view of U.S. Patent 4,810,499 ('499).

Claims 106-108, 113, 122-126, 131, 140 and 141 have been canceled and replaced with new claims. New claims 162 and 194 are directed to a method of inducing an antigen-specific immune response comprising treating an area of the skin of a subject and applying transcutaneously a formulation to the treated area of the skin of a subject. Claims 163-193 and 195 to 225 are dependent upon claims 162 and 194, respectively.

The deficiencies of '211 are discussed immediately above under the previous rejection. Delivery of antigens through the mucosal surface does not render obvious the delivery of antigens through the skin of a subject because the mucosal surface is structurally and functionally distinct from the skin, as discussed in detail immediately above. Moreover, the delivery of antigens/adjuvants through the mucosal surface is different from transcutaneous immunization which is delivery of antigens/adjuvants through the outer barrier and into the skin because the present inventors have unexpectedly found that toxic mucosal antigens/adjuvants are non-toxic when applied to the skin, as discussed above and on page 2, lines 11-22 of the specification. Further, as discussed above, the claims are directed to a method of inducing an antigen-specific immune response comprising applying a formulation transcutaneously to the skin of a subject.

The Office Action relies on the Skills Checklist for disclosing pretreatment of the skin by chemical means or by hydration means. The Advisory Action alleges that the Skills Checklist was supplied to show that pretreating the skin prior to immunization procedure is well known in the art. However, the claimed invention is directed to a method of inducing an antigen-specific immune response comprising applying transcutaneously an antigenic composition to the treated skin of a subject to induce an immune response. Neither '211 nor the Skills Checklist teaches applying transcutaneously an antigenic composition to the skin of a subject to induce an antigen-specific immune response.

Additionally, as discussed in the previous response dated March 24, 2006, it has been reported that intranasal influenza vaccine containing LT approved for distribution and use in Switzerland has been shown to cause Bell's palsy and has been withdrawn from clinical use (R.

Couch, 2004, N. Engl. J. Med., 350(9): 860; Mutsch *et al.*, 2004, N. Engl. J. Med. 350(9):896). These reports teach away from the claimed invention of using antigens/adjuvants, such as HA/LT (Example 18) and CT/Hib-PS (Example 19), for transcutaneous immunization. Accordingly, the delivery of antigens/adjuvants to the mucosal surface, such as the nasal cavity, as disclosed by '211, does not render the claimed invention obvious.

U.S. Patent '499 is relied upon for disclosing transdermal delivery. However, U.S. Patent '499 does not cure the deficiencies of '211 or of the Skills Checklist. U.S. Patent '499 does not teach transcutaneous immunization with an antigenic composition to induce an antigen-specific immune response. U.S. Patent '499 only discloses transdermal delivery of chemicals which are small molecules. Transdermal delivery of small molecules is well known and routinely practiced, but is not analogous to the present invention which is directed to transcutaneous immunization with antigen and/or adjuvant. Chemicals are small molecules of less than 500 daltons, while antigens are large molecules. As an example, CT is a protein antigen of about 85,000 daltons.

Accordingly, there is no motivation to combine the teachings of '211 and U.S. Patent '499 and to modify the method disclosed in the cited references to obtain the claimed method with any reasonable expectation of success. Thus, the cited references do not render the claimed invention obvious.

B. Claims 106-108, 113, 122-126, 131, 140 and 141 are rejected under 35 U.S.C. § 103 as being unpatentable over WO 95/17211 ('211) as evidenced by Skills Checklist for immunization, in view of U.S. Patent No. 5,814,599 ('599).

Claims 106-108, 113, 122-126, 131, 140 and 141 have been canceled and replaced with new claims. New claims 162 and 194 are directed to a method of inducing an antigen-specific immune response comprising treating an area of the skin of a subject and applying a formulation transcutaneously to the treated area of the skin of a subject. Claims 163-193 and 195-225 are dependent upon claims 162 and 226, respectively.

The deficiencies of '211 and the Skills Checklist are discussed above. U.S. Patent '599 does not cure the deficiencies of '211 because U.S. Patent '599 does not disclose applying an antigenic composition transcutaneously to the skin of a subject to induce an antigen-specific

immune response. The present invention is directed to transcutaneous immunization with antigens, while U.S. Patent '599 is directed to a method of transdermal transport of drugs.

Additionally, there is no motivation to combine the teachings of the cited references because WO '211 teaches applying a formulation to mucosal surfaces of an organism while U.S. Patent '599 teaches transdermal transport of drugs. As discussed above, the mucosal surface and the skin are structurally and functionally distinct tissues and that antigens/adjuvants that are toxic when delivered through the mucosal surface are non-toxic when applied to the skin. Moreover, '599 is not directed to inducing an antigen-specific immune response in a subject by applying an antigen transcutaneously to the skin of a subject. Thus, there is no motivation to combine the cited references and to obtain the claimed invention with any reasonable expectation of success. Accordingly, the cited references do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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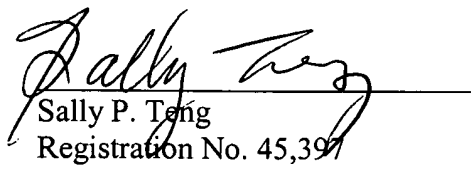

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